Case Report

Cerebral Venous Sinus Thrombosis After Gender Reassignment Surgery

Joel M. Oster, MD[1,2]; Priya Shastri, MD[2]; and Carl Geyer, MD[3]

[1]Department of Neurology, Lahey Clinic Medical Center, Burlington, Massachusetts; [2]Department of Neurology, Tufts Medical Center, Boston, Massachusetts; and [3]Department of Radiology, Lahey Clinic Medical Center, Burlington, Massachusetts

ABSTRACT

Background: Many factors have been implicated in the etiology of cerebral venous sinus thrombosis (CVT). These include head injury, cancer, infections (sepsis, sinusitis, and mastoiditis), coagulopathies, pregnancy, systemic lupus erythematosus, and dehydration.

Case summary: We present the case of a patient who received long-term estrogen therapy for ~15 years after feminizing genitoplasty. The patient experienced a CVT with an excellent clinical outcome. A similar case has not been reported in the literature.

Conclusion: Because CVT may be associated with morbidity, mortality, and risks from the complications and treatments of the condition, further research is needed to clarify the factors that may contribute to the long-term risk of CVT in patients receiving long-term estrogen therapy after feminizing genitoplasty. (*Gend Med.* 2010;7:270–275) © 2010 Excerpta Medica Inc.

Key words: stroke, venous infarct, gender reassignment surgery, feminizing genitoplasty, hormone replacement, estrogen therapy.

INTRODUCTION

Cerebral venous sinus thrombosis (CVT) results from occlusion of a venous sinus by an obstructing thrombus or an extrinsic compression.[1,2] Once the vein is occluded, the resulting venous congestion can lead to regional ischemia and infarction in the cerebral cortex. The mechanism of CVT is thought to be similar to that of deep venous thrombosis of the lower extremities, but CVT occurs with relative rarity.[3] Although both conditions are associated with thrombophilic defects, the mechanism responsible at the different sites of thrombosis is currently unknown.

Many factors have been implicated in the etiology of CVT. These include head injury, cancer, infections (sepsis, sinusitis, and mastoiditis), coagulopathies, pregnancy, systemic lupus erythematosus, and dehydration. Certain drugs have been associated with CVT, including oral contraceptives, hormone replacement therapy (HRT), estrogen therapy, androgens, and anabolic steroids.[1–4] Headache may be the only clinical sign of CVT.[5]

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By blocking venous drainage in the brain, CVT causes hemorrhagic strokes that can result in neurologic deficits, seizures, coma, and death.[1–9] Vision may be threatened from the malignant intracranial pressure that may result.[1–10] If pulmonary emboli are present with CVT, mortality is >95%.[9]

CASE SUMMARY

A 53-year-old male-to-female transsexual patient with a history of migraine and mild hypertension experienced unusual headaches for 1 week. She described a dull, throbbing, left temporal headache that was continually present, but waxing and waning in its course. Her headache was worse in the morning and had no positional component; it also had no worsening with a Valsalva maneuver. She had taken ibuprofen, which provided some relief but did not completely alleviate the headache. She had some photosensitivity with the headache but denied any vision changes, hearing loss, weakness, or numbness. These headaches were different from her migraines, which presented with a generalized dull headache associated with nausea, photophobia, and phonophobia.

The patient underwent feminizing genitoplasty in the early 1990s, and since then had been taking oral conjugated estrogens 2.5 mg daily and oral spironolactone 50 mg BID. She also occasionally took zolmitriptan for her migraines. She had no significant family history and denied tobacco, alcohol, or drug use. Physical examination revealed a pleasant, middle-aged female with normal vital signs. Head, eyes, ears, nose, and throat examinations were unremarkable, and her fundi showed no papilledema. Her cardiac sounds were regular and her lungs were clear. Her speech was fluent and revealed no aphasia. Cranial nerves were intact, and motor, reflex, sensory, cerebellar, and gait testing were all normal.

A computed tomography scan taken while in the emergency department revealed a left distal transverse sinus obstruction (**Figure 1**). The patient was admitted to the neurology service and started on intravenous heparin at 16 U/kg/hr (1200 U/hr), with the dose adjusted to prolong the prothrombin time/partial thromboplastin time to ~50 to 100 seconds, for a diagnosis of CVT. On the subsequent day, she was started on low-molecular-weight heparin at ~1 mg/kg SC twice daily, and underwent magnetic resonance imaging and venography (**Figure 2**), which confirmed the findings.

Laboratory testing showed blood chemistries and complete blood count to be normal. A hypercoagulable profile (which included factor V Leiden, prothrombin gene mutation, proteins C and S, and antithrombin III), and anticardiolipin antibody tests

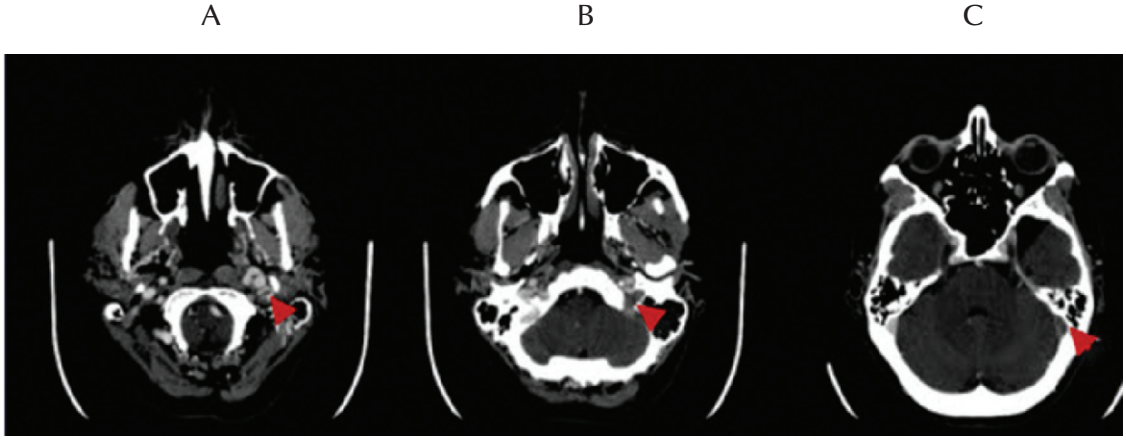

Figure 1. Initial computed tomography scan of the brain with contrast enlargement. Thrombosis is noted in the left sigmoid and transverse sinuses with filling defect in the left internal jugular venous system. Arrows delineate the findings. The image on the left (A) contains a hyperdense signal at the tip of the arrow, consistent with a subacute-to-acute thrombus. Filling defects are demonstrated in the following venous structures: (A) involves the left internal jugular vein, (B) corresponds to the sigmoid sinus, and (C) involves the sigmoid–transverse sinus junction.

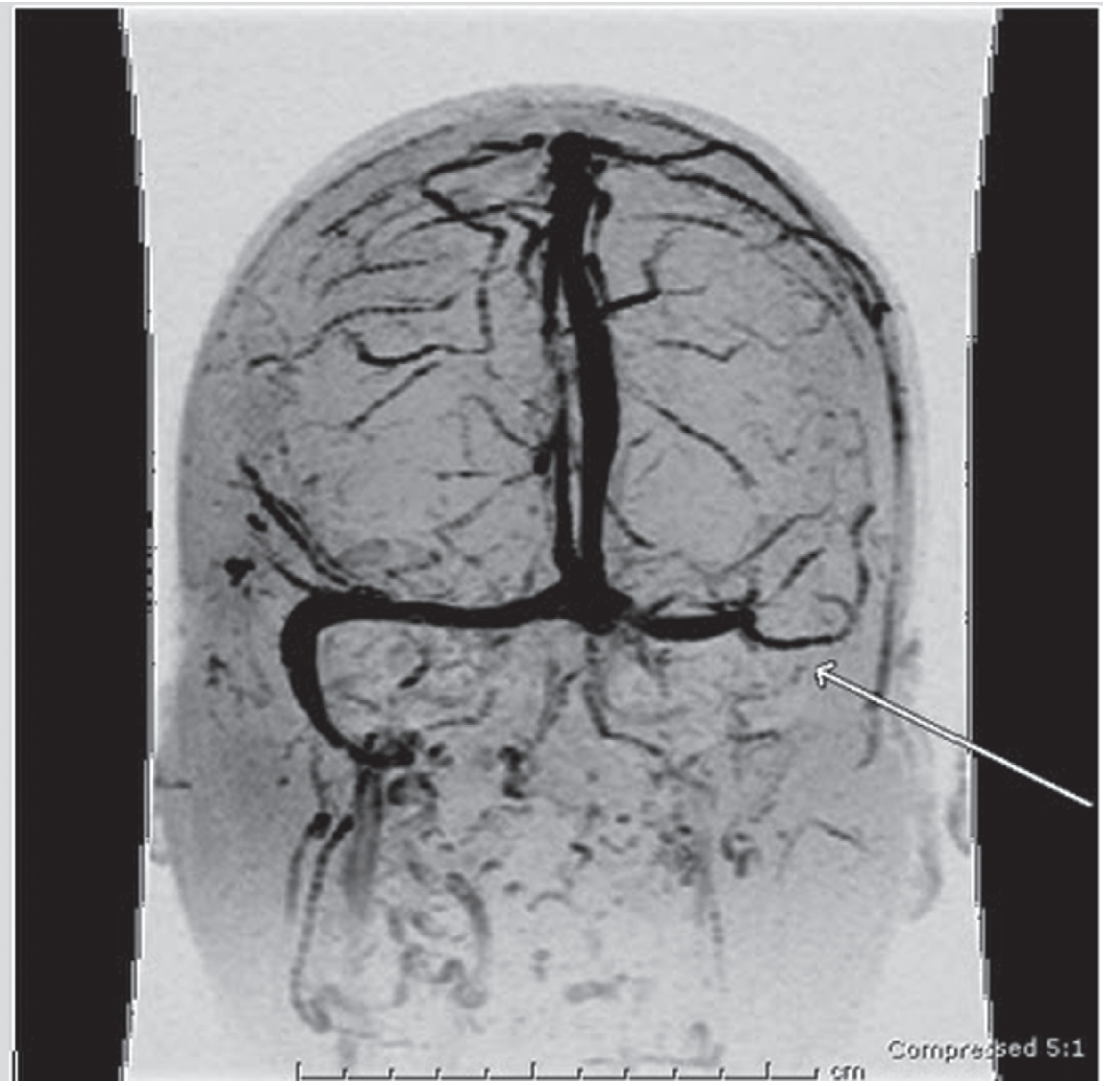

Figure 2. Magnetic resonance venography performed the day after admission shows slow flow versus thrombosis in the left sigmoid and transverse sinuses and left internal jugular venous system. An arrow delineates the findings.

and titers were normal. The patient had a positive lupus anticoagulant, which was repeated ~2 months after hospital discharge and remained positive. Transesophageal echocardiography did not reveal any evidence of either a cardiac thrombus or a cardiac source of thrombus, and lower-extremity Doppler ultrasound was negative for deep venous thrombosis. The patient had not had a cerebral infarction or hemorrhage.

The patient's headache was treated conservatively with acetaminophen, and she was transitioned to warfarin for the long term (ultimately, 5 mg PO daily) after starting low-molecular-weight heparin as noted. We recommended discontinuing the estrogen therapy. Computed tomography angiography of the venous system at ~10 months is shown in **Figure 3**. While the patient's neurologic exam remains normal ~3 years after the thrombosis, the CVT did not recanalize, and she has elected to continue taking warfarin.

DISCUSSION

Treatments for CVT include intravenous heparin, oral anticoagulants, and thrombolysis.[1–9] Treating

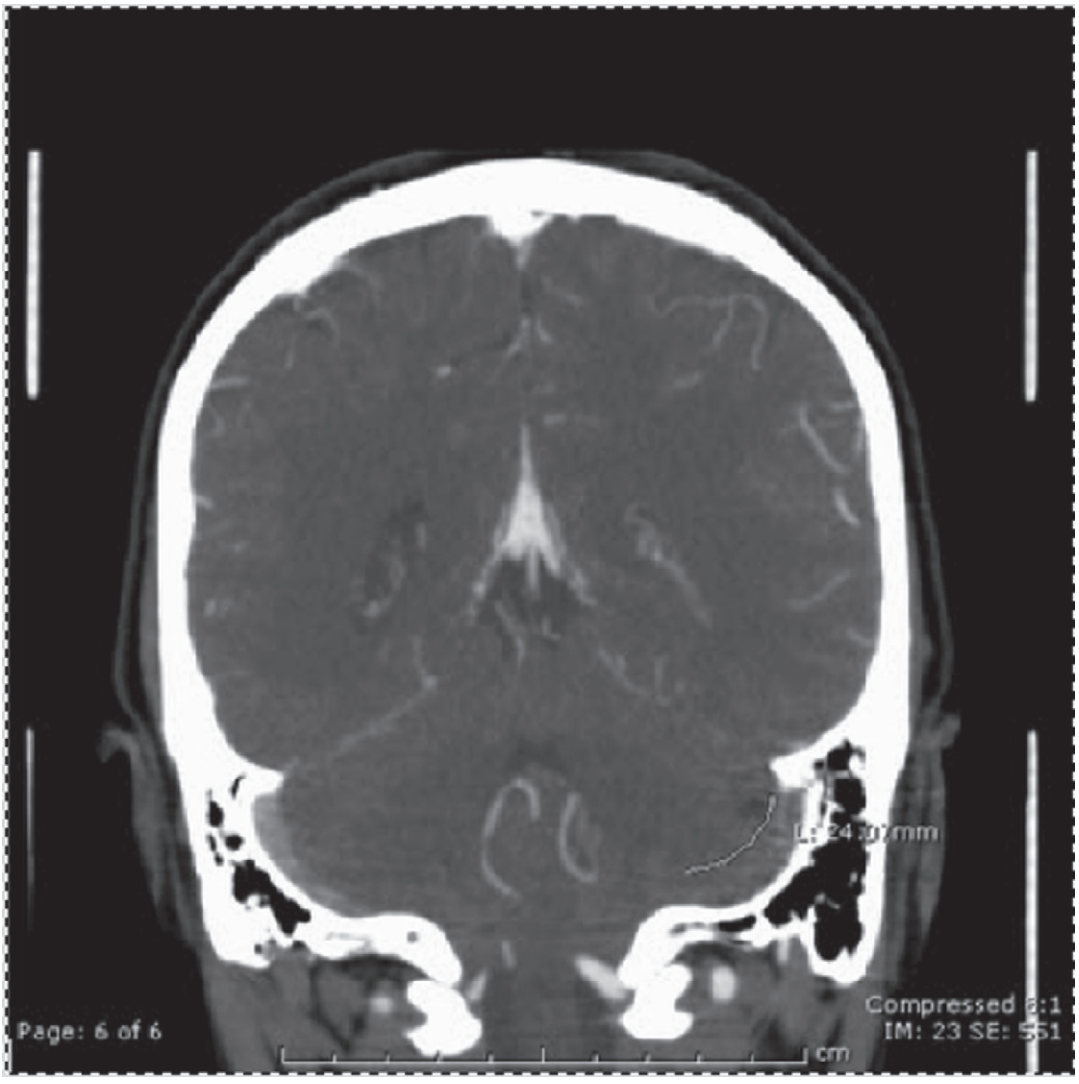

Figure 3. Follow-up computed tomography angiography delineating lack of contrast uptake in the left sigmoid and transverse sinuses and left internal jugular venous system ~10 months later. Curvilinear marking outlines these findings.

seizures and elevated intracranial pressure (and the possible resulting hemorrhage) is part of the management of CVT. Although hemorrhage may occur in association with CVT, anticoagulants seem to be required in many cases and may be necessary, even when there is hemorrhage present, for optimal outcome.[8] Risks are entailed with the treatment of CVT, not only with thrombolytic therapy, which is associated with causing or worsening intracranial hemorrhages, but also with interventional approaches to stroke care, in which major complications may occur in association with cerebral angiography.[10–12] In untreated cases of CVT, mortality has been reported in the range of 13.8% to 48%.[6,7,9] Of those who survive, between 25% to 30% of patients have a full recovery.[6,7,10] Buccino et al[7] noted a good clinical outcome in their follow-up of 34 patients with confirmed CVT in 2003. In that study, however, the investigators did find that 30% of the patients experienced episodic headaches, 8.8% had seizures, 11.7% had pyramidal signs, 5.9% had visual deficits, and 17.6% had working memory deficits and depression.

CVT is a well-known consequence of the use of estrogen and estrogen–progestin oral contraceptives, because estrogen has effects on the production of clotting factors II, VII, IX, and X; antithrombin III; and tissue plasminogen activator.[13–15] However, the association between postmenopausal HRT and CVT is not well documented, although the review of a few cases by Vander et al[16] seemed to indicate that HRT is not an independent risk factor for CVT. An association between HRT or estrogen therapy and CVT in a postfeminizing genitoplasty population receiving chronic treatment with estrogens has not been described previously in the literature (English-language, MEDLINE-indexed journals). One recent review concluded that screening for activated protein C resistance, antithrombin III, free protein S antigen, and protein C deficiency in transsexual patients is generally not recommended.[17]

While the literature does note both the association of stroke with HRT (which was not exactly the situation of this patient, who began taking oral conjugated estrogen in her late thirties) and the presence of lupus anticoagulant as a risk factor for thrombosis, the reason why this patient remained symptom free for 15 years and then had thrombosis is uncertain.[18,19] We speculate that 15 years of estrogen administration, increasing age, and the presence of lupus anticoagulant could have been contributing factors, although the remainder of the mechanism responsible for the CVT is unknown. Our case report suggests that further study is needed to clarify the factors that contribute to the long-term risk of CVT in patients who are prescribed long-term estrogen therapy after feminizing genitoplasty.

CONCLUSION

Because CVT may be associated with morbidity, mortality, and risks from the complications and treatments of the condition, further research is needed to clarify the factors that may contribute to the long-term risk of CVT in patients receiving long-term estrogen therapy after feminizing genitoplasty.

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Address correspondence to: Joel M. Oster, MD, Department of Neurology, Lahey Clinic Medical Center, 41 Mall Road, Burlington, MA 01805. E-mail: Joel.M.Oster@lahey.org